DYNAVAX TECHNOLOGIES CORPORATION

VRBPAC Meeting
November 15, 2012

Errata and Clarifications to the Sponsor Briefing Document
BLA # 125428 (HEPLISAV™)

1. Page 13 of Section 1.2 Medical Need for an Improved Hepatitis Vaccine, at the end of the first paragraph:

   The currently approved hepatitis B vaccines (Engerix-B and Recombivax®) have provided significant benefits, but they have limitations that reduce their effectiveness in adults, both in terms of their administration and.

Should be corrected to:

   The currently approved hepatitis B vaccines (Engerix-B and Recombivax®) have provided significant benefits, but they have limitations that reduce their effectiveness in adults, both in terms of their administration and ***immunogenicity****.*

2. Page 21 of Section 1.5 Safety, at the end of the first paragraph:

   In DV2-HBV-10, the rates of autoimmune adverse events ~~***(AIAEs)***~~ *were 2 of 1809 (0.11%) subjects in HEPLISAV recipients and 1 of 606 (0.17%) subjects in Engerix-B recipients* ~~***and in the entire program,***~~ *the rates of* ~~***AIAEs***~~ *were 7 of 2500 (0.28%) subjects in HEPLISAV recipients and 4 of 930 (0.43%) subjects in Engerix-B recipients (RR: 0.65; 95% CI: 0.19, 2.22).*

Should be corrected to:

   In DV2-HBV-10, the rates of autoimmune adverse events were ***5*** *of 1809 (****0.28****%) subjects in HEPLISAV recipients and* ***3*** *of 606 (****0.50****%) subjects in Engerix-B recipients****. In the supporting trials, 3 additional events were identified: 2 in HEPLISAV recipients and 1 in Engerix-B recipients. In the clinical development program through DV2-HBV-10****, the rates of* ***autoimmune adverse events*** *were 7 of 2500 (0.28%) subjects in HEPLISAV recipients and 4 of 930 (0.43%) subjects in Engerix-B recipients (RR: 0.65; 95% CI: 0.19, 2.22).*

3. Page 60 of Section 6.1 Overview of Safety, at the start of the fourth paragraph:

   HEPLISAV and Engerix-B had similar rates of post-injection reactions (HEPLISAV: 55.1%; Engerix-B: 57.1%) as well as local post-injection reactions (HEPLISAV: 42.8%; Engerix-B: 41.1%) and systemic post-injection reactions (HEPLISAV: 32.3%; Engerix-B: ~~***25.1***~~*%).*

Should be corrected to:

*HEPLISAV and Engerix-B had similar rates of post-injection reactions (HEPLISAV: 55.1%; Engerix-B: 57.1%) as well as local post-injection reactions (HEPLISAV: 42.8%; Engerix-B: 41.1%) and systemic post-injection reactions (HEPLISAV: 32.3%; Engerix-B: **37.4**%).*

4. Page 63 of Section 6.2 Autoimmune Considerations, at the third paragraph:

There is no known association between the humoral response to HBsAg and any particular autoimmune disease.

*To explore this possibility, Dynavax reviewed all AEs of autoimmune disease in DV2-HBV-10, and in the entire HEPLISAV development program **to date**.*

*In the clinical development program **to date**, the rates of autoimmune adverse events were 7 of 2500 (0.28%) subjects in HEPLISAV recipients and 4 of 930 (0.43%) subjects in Engerix-B recipients (RR: 0.65; 95% CI: 0.19, 2.22).*

Should be corrected to:

*There is no known association between the humoral response to HBsAg**, 1018 ISS Adjuvant, or a TLR9 agonist**, and any particular autoimmune disease.*

*To explore this possibility, Dynavax reviewed all AEs of autoimmune disease in DV2-HBV-10, and in the entire HEPLISAV development program **prior to DV2-HBV-10**.*

*In the clinical development program **through trial DV2-HBV-10**, the rates of autoimmune adverse events were 7 of 2500 (0.28%) subjects in HEPLISAV recipients and 4 of 930 (0.43%) subjects in Engerix-B recipients (RR: 0.65; 95% CI: 0.19, 2.22).*

5. Page 79 of Section 6.5.1 Summary of Autoimmune Adverse Events, the second, third and fourth bullet points:

- ~~***There was no difference between HEPLISAV and Engerix-B with respect to either overall autoimmune safety findings or e***~~*xacerbations of PEAI disease in subjects identified with pre-existing events of special interest (HEPLISAV: 2.3%; Engerix-B: 4.3%).*
- ~~***In DV2-HBV-16, 3 new-onset autoimmune AEs were identified in 1968 HEPLISAV subjects and 0 in 481 Engerix-B subjects***~~*.*

- *Rates change~~s~~ in autoantibodies (ANA, anti-dsDNA, ANCA) were similar for HEPLISAV and Engerix-B subjects. For all trials, rates of development of autoantibodies were similar between recipients of HEPLISAV ~~**or HEPLISAV (All)**~~ and recipients of Engerix-B, including ANA (HEPLISAV: 5.7%; Engerix-B: 5.3%), and anti-dsDNA (HEPLISAV: 1.~~**6**~~%; Engerix-B: ~~**1.8**~~%). Retrospective testing for ANCA revealed no additional subjects with ANCA antibody in either treatment group beyond the 2 subjects with ANCA-associated vasculitis in DV2-HBV-10.*

Should be corrected to:

- ***E****xacerbations of PEAI disease in subjects identified with pre-existing events of special interest* ***were also similar*** *(HEPLISAV: 2.3%; Engerix-B: 4.3%).* (Comment: Modified as statement is repeated in the fifth bullet point.)

- *Two events in DV2-HBV-16 were adjudicated as autoimmune events by the SEAC that were not already identified as AESIs in the HEPLISAV group (2 of 1968 subjects or 0.1%) and zero in the Engerix-B group (0 of 481 subjects or 0.0%).*

- *Rates* ***of*** *change in autoantibodies (ANA, anti-dsDNA, ANCA) were similar for HEPLISAV and Engerix-B subjects. For all trials, rates of development of autoantibodies were similar between recipients of HEPLISAV and recipients of Engerix-B, including ANA (HEPLISAV: 5.7%; Engerix-B: 5.3%), and anti-dsDNA (HEPLISAV: 1.****2****%; Engerix-B: ****0.9****%). Retrospective testing for ANCA revealed no additional subjects with ANCA antibody in either treatment group beyond the 2 subjects with ANCA-associated vasculitis in DV2-HBV-10.*

6. Page 88 of Section 6.5.5.3 Anti-neutrophil Cytoplasmic Antibodies, in the first paragraph:

   *A total of 3 of 1780 HEPLISAV subjects (0.17%) and 2 of 96 Engerix-B subjects (0.34%) had a positive ~~**screening**~~ ELISA; all were positive before vaccination.*

Should be corrected to:

A total of 3 of 1780 HEPLISAV subjects (0.17%) and 2 of 96 Engerix-B subjects (0.34%) had a positive ELISA ***prior to vaccination****; all were positive before vaccination.*

7. Page 91 of Section 7.1.2 Demonstrated Benefits, in the first paragraph:

   *Two doses of HEPLISAV over 1 month met not only the primary objective of noninferiority in the 2 pivotal phase 3 trials but also demonstrated that HEPLISAV induced significantly higher ~~**antibody levels**~~ than Engerix-B.*

Should be corrected to:

Two doses of HEPLISAV over 1 month met not only the primary objective of noninferiority in the 2 pivotal phase 3 trials but also demonstrated that HEPLISAV induced significantly higher ***seroprotection rates*** *than Engerix-B.*

8. Page 91 of Section 7.1.3 Potential Benefits, in the first paragraph:

Combining adherence data from VSD Study with SPR data from clinical trials ~~***results in***~~ *the effective SPR; that is, the SPR* ~~***expected in the real world. In the VSD Study of over 880000 enrollees in medical care organizations, adherence ranged from 74.3% of adults 18 to 29 years of age receiving 2 doses of hepatitis B vaccine and 53.1% receiving 3 doses of 84.9% of adults 50 to 64 years of age and older receiving 2 doses and 71.2% receiving 3 doses. Using adherence rates from VSD Study and SPRs from the pooled mITT population in the Dynavax pivotal phase 3 trials,***~~ *it may be expected that the effective SPRs in the HEPLISAV groups are similar in all 3 age groups (83% to 84%) while the effective SPRs in the Engerix-B groups decrease from 63% in the youngest age group to 55% in the oldest age group. The difference in effective SPRs between the HEPLISAV and Engerix-B groups ranges from 20% to 28% (Appendix 3).*

Should be corrected to:

Combining adherence data from ***the*** *VSD Study with SPR data from clinical trials* ***gives*** *the effective SPR; that is, the SPR* ***anticipated in actual use. I****t may be expected that the effective SPRs in the HEPLISAV groups are similar in all 3 age groups (83% to 84%) while the effective SPRs in the Engerix-B groups decrease from 63% in the youngest age group to 55% in the oldest age group. The difference in effective SPRs between the HEPLISAV and Engerix-B groups ranges from 20% to 28% (****for details see*** *Appendix 3).*